Hormone Therapy in Relation to Survival from Large Bowel Cancer

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Abstract

Epidemiologic studies of hormone therapy (HT) and colorectal cancer incidence consistently show an inverse association; however, few studies considered prediagnostic use of HT on mortality among colorectal cancer patients. We evaluated the relationship of HT and survival among a population-based cohort of women with large bowel cancer. Cases (n=1297) were newly diagnosed with invasive cancer of the colon or rectum, aged 40-74 years at diagnosis, who were identified by Wisconsin's statewide registry (1988-1991; 1997-2001) for two case-control studies. Information on HT use and other colorectal cancer risk factors was collected by standardized interview. There were 507 deaths (274 of these attributable to colorectal cancer) over 8.4 years of follow-up through December 2005. Hormone use was not associated with colorectal cancer mortality (Adjusted hazard rate ratio=1.09, confidence interval=0.81-1.47). Colorectal cancer specific mortality was not associated with HT when considered separately by preparation type or combined. Stage did not modify this relationship. Long-term HT was weakly positively associated with increased mortality after diagnosis of proximal colon, but not distal colon cancer. Because we detected no differences in survival among users of HT compared to non-users, the results suggest that HT use may affect the incidence of only some colorectal tumors.

Introduction

Hormones clearly play a role in large bowel health, both through direct and indirect mechanisms[1]. Observational studies and randomized controlled trials of colorectal cancer have been remarkably consistent in demonstrating 20-40% reduction in risk in current users of hormone therapy (HT) [2-11], including an almost 40% reduction in risk that was reported for current HT use in a randomized controlled trial [5, 12]. It is not clear, though, what effects the use of prediagnostic hormone therapy may have on subsequent mortality after colorectal cancer diagnosis. Two cohort studies in women with colorectal cancer, who were then followed-up for mortality, have observed associations between HT use and reduced risk of death from colorectal cancer, although associations within subsite were inconsistent [13, 14]. These studies were unable, however, to adjust for several important confounders, including screening [13, 14]. In a large cohort of healthy women, HT use was associated with a reduced risk of colorectal cancer mortality [15], but this design could not distinguish HT effects on incidence from those of survival. More recently, results from a HT trial indicated no association between conjugated equine estrogens and colorectal cancer mortality, though numbers of deceased women were small: 20 and 16 women deceased for the intervention and placebo groups, respectively [16]. Although many women have discontinued use of HT following the publication of the results of recent HT trials [7, 17], nearly 50% of women aged 50-65 years have ever used HT, and about 12% still continue to do so [18]. We had an opportunity to evaluate the relationship between HT and mortality in a cohort of colorectal cancer cases based upon our earlier case-control studies of colorectal cancer in women [8, 19].

Materials and Methods

This analysis was conducted using pooled data from two case-control studies that used similar designs and questionnaires. Both studies were approved by the Institutional Review Board at the University of Wisconsin-Madison in accord with assurances filed with and approved by the U.S. Department of Health and Human Services.

Identification of cases

This study retrospectively followed all cases who were enrolled in our previous case-control studies, which included female Wisconsin residents, ages 40-74 years, with an incident diagnosis of colorectal cancer during two periods: from 1988-1991 and 1997-2001. These studies have been previously described in detail, including differences in baseline characteristics between the two study phases [19, 20]. Briefly, diagnostic reports, including information on cancer site, histology, extent of disease, and follow-up physician, were obtained from Wisconsin's mandatory population-based cancer registry. Eligibility for the case-control study was limited to cases with listed telephone numbers and without prior diagnosis of colorectal cancer. The physician of record for each eligible case was contacted by mail to request permission to contact the woman. Of the 2,209 eligible cases, physicians refused contact for 129 (6%), 370 (17%) were found to be deceased, 211 (9%) refused to participate, 26 (1%) were unable to be located, and 4 (0.2%) interviews were deemed unreliable. Thus, data for 1,469 women were collected, with similar response rates in the two time periods, and for an overall response rate of 67%. Cases under the age of 40 years (n=31) or with incomplete information on hormone therapy use (n=90) were excluded from the analysis; therefore 1,348 cases were included in this study. The following classifications were used for colon subsite analyses: cancer of the proximal colon

included sites from the cecum to the tranverse colon (International Classification of Diseases for Oncology (ICD-O) codes C18.0-18.4 [21]), and cancers of the distal colon included sites from the splenic flexure to the rectum (ICD-O codes: C18.5-C18.7, C19.9). Multiple and not otherwise specified (NOS) sites (ICD-O codes: C18.8-9) were excluded from subsite analyses. Extent of disease was reported by the registry as local, regional, distant, or unknown.

Data collection

All cases completed a standardized 40-minute telephone interview that elicited information on use of HT. Only exposures prior to diagnosis were included by asking women to report exposures occurring in the year prior to diagnosis or on average two years prior to interview. There were slight variations in the questionnaire format for the two study periods; all versions elicited a standard history of HT, including types, duration, age at initial use, and time since last use. HT use was defined as the use of oral, injectable, or transdermal non-contraceptive hormones for 3 months or more. Other risk factors for colorectal cancer were also collected, including reproductive and menstrual history, physical activity, current and past height and weight, medication use, screening by endoscopy and/or fecal occult blood test, family history of colorectal cancer, alcohol consumption, smoking history, medical history, and demographic data. Information about the cases' personal and family history of colorectal cancer was obtained at the end of the interview to maintain blinding. The interviewers were unaware of the disease status of the subjects until the end of the interview for 78% of cases.

Identification of deaths

Outcomes that occurred after the completion of a case's interview and before the end of follow-up on December 31, 2005 were included. The vital status of study participants was determined using name, date of birth, and social security number (when available) to link with death records. First, the death certificate data from the Wisconsin Vital Records Office were searched for deaths. For cases not reported to be deceased in the state vital records, we used automated linkages with the National Death Index [22]. For all deaths, we ascertained underlying cause of death, assigned according to the International Classification of Diseases Tenth Revision. The primary endpoint was death from colon cancer (ICD-10 codes C18-C20, C26.0), but we also examined death from any cause. When there was a discrepancy between anatomic site between death certificate and cancer registry data, we assigned the anatomic site at death to that reported by cancer registry, because cause of death may be misclassified on death certificates.

Statistical analyses

For women who were deceased, survival was calculated as the number of months from date of diagnosis to date of death. For all other women, survival was censored on December 31, 2005. Cox proportional hazards models were used to estimate the adjusted hazard rate ratio (HRR) and corresponding 95% confidence intervals for colorectal and all-cause mortality according to HT use [23]. HT use was characterized as "any use", exclusive use of estrogen–alone, and exclusive use of estrogen-progestin. We examined use according to any use ("ever"), recency (current or former) and total duration of use. "Any" HT use included exclusive estrogen-alone and estrogen-progestin users as well as women who used both types of preparations at various times. A woman was defined as a current user of HT if she reported use in the calendar year before the

diagnosis. Women were classified as postmenopausal if they reported having a natural menopause or hysterectomy with bilateral oophorectomy by the date of diagnosis. Women who underwent hysterectomy without bilateral oophorectomy were considered postmenopausal if they reached the age at which natural menopause occurred in 90% of the cohort (54.4 years for smokers, 55 years for non-smokers).

There were differences between the two study phases for some baseline characteristics; oral contraceptive use and body mass index were higher for both cases and controls in the second phase, and screening was higher in the second phase for cases only [19]. Thus, all regression models were stratified on phase of study and exact age at diagnosis. Confounders, chosen *a priori*, that were adjusted for in multivariable models included body mass index (by quartiles in kg/m^2), menopausal status, endoscopy screening history (never, ever), smoking status (never, ever), and family history of cancer (absent, present), and time from date of diagnosis to interview. Additional exploratory analyses were conducted to examine whether age at diagnosis (<70 versus ≥ 70 years), stage of disease (localized versus regional/distant), and endoscopy screening history (no versus yes) modified these associations. All analyses were performed using SAS 9.1 software (SAS Institute, Inc., Cary, NC).

Results

Women using HT were more likely to be younger, have localized disease, were slightly leaner, and ever smokers (Table 1) compared to non-users. Approximately 40% of HT users reported a history of regular endoscopy screening, compared with only 32% of non-users.

After a mean follow-up of 8.4 years (range 1-18 years), there were 507 deaths, with 274 attributed to colon or rectal cancer. Overall there was no association between use of HT and colorectal cancer mortality (Table 2). No associations were observed between recency of use and colorectal cancer mortality in either current users (HRR=1.25, 95% CI 0.87-1.81) or former users (HRR=0.87, 95% CI, 0.55-1.35). Increasing time (per year) since last use of HT was associated with a modest reduction in risk (HRR=0.95, 95% CI, 0.91-0.99), although no trends were observed with increasing duration of use (HRR=1.01 (per year), 95% CI, 0.99-1.04). Neither exclusive estrogen–alone, nor estrogen–progestin preparations were associated with colorectal cancer mortality.

The results from analyses stratified by site of colorectal cancer were similar to the overall colorectal cancer mortality results (Table 2). However, among proximal colon cancer cases, an increased risk of mortality was associated with increasing duration of HT use compared to HT non-users (HRR=1.04 per year, 95% CI, 1.00-1.07). However, when examining time since last use of HT, a reduction in risk was observed with a 0.87 reduction in risk for each additional year since last use (95% CI, 0.78-0.98). These site-specific risks did not appear to differ by type of HT preparation, and no associations were observed among distal colon cases. Risks also appeared to be similar by extent of disease, although small numbers of deaths occurring among women with localized disease limited this analysis.

Death from any cause was not related to use of HT, with no differences in risk comparing HT users with non-users (HRR=0.87, 95% CI 0.69-1.09). The associations with HT and all-cause mortality, stratified by site of initial cancer, were similar to those overall (Table 3). Again,

among proximal colon cancer cases there was a suggestion of an increased risk of death from all-causes associated with increasing years of HT use (HRR=1.03, 95% CI, 1.00-1.06, Table 3). There was no association between HT among women diagnosed with distal colon cancer, nor were there statistically significant associations between type of HT used, and all-cause mortality.

Age at diagnosis, stage of disease, and history of screening did not modify these associations, and no associations were statistically significant after stratifying by these variables. The risk of colorectal cancer mortality associated with HT use was 0.63 (95% CI, 0.27-1.44) among women who had localized disease ($n_{deceased}$=8), and 1.17 (95% CI, 0.84-1.64) among women with regional/distant disease ($n_{deceased}$=51). The risk of colorectal cancer mortality associated with HT use was 0.92 (95% CI, 0.62-1.36) among women who had not been screened ($n_{deceased}$=35), and 1.40 (95% CI, 0.83-2.37) among women who were screened ($n_{deceased}$=26).

Discussion

In this population-based study we did not observe any associations between HT and the risk of colorectal cancer mortality or all-cause mortality, regardless of its definition. Among women with proximal colon cancer diagnoses, a modest increased risk of both colorectal cancer and all-cause mortality was observed among long-term users of HT that was attenuated with increasing time since last use of HT. Our confidence in these study results is enhanced by the population based nature of our study, and our ability to adjust for important confounders not available in prior studies, especially screening history.

Our results appear to be in contrast with previous studies of HT use and colon cancer mortality in two previous cohorts of cases; both found inverse relationships between HT use prior to diagnosis and mortality[13, 14]. Slattery *et al*. found that, after a mean 7 years of follow-up after colon cancer diagnosis, women who had ever used HT had a statistically significant 40% lower risk of colorectal cancer mortality than non-users [14]. Similarly, Mandelson *et al*., after 6 years of follow-up, also showed a reduction in mortality associated with HT use, although this reduction appeared to be limited to lesions in the distal colon (hazard ratio=0.33, 95% CI, 0.13-0.83) [13]. Notably, neither study adjusted for history of endoscopy screening. These effects of screening on colorectal cancer prognosis make this a potentially important confounder in epidemiologic studies of colorectal cancer. In a *post-hoc* analysis, although our study did not find differences in risk when screening was removed from our models, we did observe that HT users were more likely to have been screened and been diagnosed with more localized cancers that non-HT users. Women with a history of screening were also more likely to have localized disease (45% and 40% of women diagnosed with localized disease for screened and unscreened, respectively). Additionally, the Mandelson *et al.* study [13] relied on linkages of pharmacy records to medical records, and thus it was not possible to adjust for other potential important correlates of HT, such as body mass index. In prior studies examining overall mortality among cohorts of healthy women, the relationship with HT use has been modestly inverse, with the greatest reductions in risk among current HT users [15, 24-26]. Such a finding is likely consistent with the strong reductions in incidence associated with current HT use, which is impossible to separate from an association with mortality in this design.

Based upon these limited studies and contradictory results, it is difficult to reach a consensus on the relationship between HT use and colorectal cancer mortality. There is some evidence that the association between HT and colorectal cancer incidence varies by stage of disease. In the Women's Health Initiative (WHI) trial, women who used estrogen plus progestin were more likely to be diagnosed at an advanced stage of disease (i.e. regional or metastatic) than cases in the placebo arm (76.2% vs. 48.5%, p=0.004, ref.[5]). After adjustment for stage at diagnosis, no increased or decreased risk of colorectal cancer mortality was observed among our cohort of women. Thus our results appear to be consistent with this randomized controlled trial.

When interpreting the results of this study, several limitations should be considered. We measured HT use 1-2 years prior to diagnosis, and did not evaluate HT use after diagnosis. Thus, there could be some misclassification of the exposure if women who were non-users initiated HT use after their colorectal cancer diagnosis, or selectively continued HT use. Such treatment patterns would be relatively unlikely since, in general as a promoter, HT is often contraindicated after a diagnosis of some cancers because of its growth promoting properties [27]. We were unable to interview all eligible cases, and 17% of women were deceased before we could enroll them. The loss of subjects due to death is always raises concerns about the possibility of survival bias. However, the results of our case-control study, upon which this study is based, found a strong inverse association with HT that was consistent with the findings of other prospective studies, as well as the Women's Health Initiative, where losses to death were not an issue [2-11]. Women in the study who reported use of HT, however, were actually slightly more likely than non-users to be diagnosed at an earlier stage, so bias towards the null due to advanced stage appears unlikely to explain these results. In addition, our previous study of body mass and

colorectal cancer mortality [20], found no differences in associations with mortality among the different stages of cancer diagnoses. Finally, our sample sizes for several subcategories were quite small, thus limiting our ability to detect some associations of interest, and limiting our ability to assess effect modification; these results may also be due to chance due to the limited power and multiple comparisons.

There is ample biologic plausibility that estrogens may exert an effect on colorectal cancer incidence [1], possibly through several mechanisms. Indeed, the colon contains hormone receptors that are likely pivotal in its responsiveness to sex hormones[28]. However, the mechanisms by which HT use might impact survival remain poorly studied. In our study, women who developed incident proximal colon cancer even while using HT prior to diagnosis may have developed tumors resistant to the benefits of HT. If these women develop colon cancer despite exogenous estrogen use, other genetic or environmental factors predisposing women to colorectal cancer may predominate. The presence of differential etiologic pathways predominating in users versus non-users of HT by colon cancer site needs to be explored, in the laboratory, clinic, and population.

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Table 1. Baseline characteristics of postmenopausal women with incident colorectal cancer, Wisconsin (1988-91 and 1997-2001).

	Never used hormone therapy (N=992)		Ever used hormone therapy (N=356)	
	n	%	n	%
Age at diagnosis				
40-54	166	16.7	64	18.0
55-59	108	10.9	55	15.4
60-64	167	16.8	60	16.9
65-70	269	27.1	91	25.6
70-74	282	28.4	86	24.2
Cancer site				
Colon	815	82.2	299	84.0
Rectum	177	17.8	57	16.0
Extent of disease/stage				
Local	392	39.5	171	48.0
Regional	476	48.0	150	42.1
Distant	79	8.0	20	5.6
Unknown	45	4.5	15	4.2
Body mass index (kg/m2)				
<22.5	236	23.8	90	25.3
22.5-25.4	226	22.8	92	25.8
25.5-28.9	245	24.7	92	25.8
≥29.0	266	26.8	81	22.8
Family history of colorectal cancer				
No	767	77.3	279	78.4
Yes	179	18.0	68	19.1
Unknown	46	4.6	9	2.5
Smoking status				
Never	517	52.1	160	44.9
Former	263	26.5	134	37.6
Current	206	20.8	62	17.4
History of endoscopy screening				
No	661	66.6	213	59.8
Yes	315	31.8	142	39.9
Unknown	16	1.6	1	0.3

Table 2. Colorectal cancer mortality in women by use of hormone therapy and cancer site

	Colorectal cases			Colon cases			Proximal Colon cases			Distal Colon cases			Rectal cases		
Hormone Therapy	Number of Deaths	HRR*	95%CI	Number of Deaths	HRR*	95%CI	Number of Deaths	HRR*	95%CI	Number of Deaths	HRR*	95%CI	Number of Deaths	HRR*	95%CI
Never†	213	1.00	reference	172	1.00	reference	58	1.00	reference	101	1.00	reference	41	1.00	reference
Ever	61	1.08	0.80-1.46	48	1.03	0.73-1.45	21	0.99	0.56-1.74	20	0.90	0.53-1.53	13	1.26	0.58-2.71
Former	21	0.87	0.55-1.35	17	0.87	0.52-1.46	7	0.71	0.31-1.61	8	0.98	0.46-2.12	4	0.77	0.23-2.51
Current	40	1.25	0.87-1.81	31	1.16	0.76-1.77	14	1.34	0.66-2.73	12	0.84	0.43-1.63	9	1.81	0.71-4.58
Duration of Use in Years															
<5	29	1.08	0.72-1.61	21	0.94	0.59-1.50	7	0.82	0.21-1.27	10	0.98	0.49-1.96	8	1.42	0.54-3.74
≥5	32	1.08	0.73-1.60	27	1.12	0.72-1.74	14	1.53	0.82-3.10	10	0.82	0.41-1.66	5	1.09	0.38-3.14
Continuous, per year		1.01	0.99-1.04		1.01	0.98-1.04		1.04	1.00-1.07		0.98	0.92-1.03		1.02	0.95-1.08
p-value			0.44			0.54			0.04			0.37			0.63
Type of Treatment															
Estrogen only	41	1.18	0.53-1.68	34	1.16	0.78-1.71	13	0.83	0.42-1.64	15	1.28	0.71-2.33	7	1.17	0.46-2.95
Estrogen/Progestin	13	1.13	0.63-2.04	9	0.94	0.46-1.92	6	2.31	0.89-5.99	2	0.3	0.07-1.33	4	3.32	0.62-17.82
Other/Unknown	7	0.68	0.31-1.45	5	0.65	0.27-1.62	2	0.71	0.16-3.12	3	0.67	0.21-2.19	2	0.87	0.19-3.95

* Proportional hazards models stratified on phase of study and age at diagnosis, and adjusted for menopausal status, body mass index, extent of disease screening, smoking status, family history of colorectal cancer, and time from date of diagnosis to interview.

† Reference category.

Table 3. All-cause mortality in women by use of hormone therapy and cancer site

	Colon cases			Proximal colon cases			Distal colon cases			Rectal cases		
Hormone Therapy	Number of Deaths	HRR*	95%CI	Number of Deaths	HRR*	95%CI	Number of Deaths	HRR*	95%CI	Number of Deaths	HRR*	95%CI
Never†	329	1.00	reference	127	1.00	reference	183	1.00	reference	79	1.00	reference
Ever	80	0.88	0.68-1.14	38	0.92	0.62-1.37	34	0.76	0.51-1.12	19	0.77	0.43-1.37
Former	39	0.89	0.63-1.25	19	0.87	0.48-1.34	18	0.92	0.55-1.53	8	0.55	0.25-1.24
Current	41	0.87	0.61-1.24	19	0.98	0.63-1.91	16	0.63	0.36-1.09	11	1.09	0.51-2.30
Duration of Use in Years												
<5	40	0.95	0.68-1.34	18	1.03	0.50-1.45	18	0.86	0.52-1.44	13	0.97	0.49-1.95
≥5	40	0.82	0.58-1.15	20	1.08	0.59-1.68	16	0.67	0.39-1.14	6	0.55	0.22-1.33
Continuous, per year		0.99	0.97-1.02		1.03	1.00-1.06		0.97	0.93-1.01		0.98	0.93-1.04
p-value			0.59			0.08			0.10			0.58
Type of Treatment												
Estrogen	53	0.91	0.67-1.22	24	0.82	0.51-1.32	22	0.85	0.53-1.37	9	0.60	0.28-1.26
Estrogen/Progestin	11	0.64	0.34-1.20	7	1.41	0.62-3.23	3	0.28	0.09-0.91	5	2.36	0.66-8.42
Other/Unknown	16	1.03	0.62-1.71	7	0.99	0.44-2.20	9	1	0.50-1.99	5	0.79	0.29-2.14

* Proportional hazards models stratified on phase of study and age at diagnosis, and adjusted for menopausal status, body mass index, extent of disease screening, smoking status, family history of colorectal cancer, and time from date of diagnosis to interview.

† Reference category.